

# Perioperative hemodynamic instability in patients undergoing laparoscopic adrenalectomy for pheochromocytoma

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**Abstract:** Perioperative hemodynamic instability still remains the biggest surgical and anesthetic challenge in surgery for pheochromocytoma. The aim of this review was to discuss pre-, intra- and postoperative factors that may impact on hemodynamic condition of a patient. It describes patients' preparation with appropriate medication, principles of surgical technique as well as risk factors for development of hemodynamic instability in postoperative period. Currently the gold standard in the treatment of pheochromocytoma is preoperative use of alpha-blockers and laparoscopic surgery. This approach allowed improving outcomes by lowering both mortality and morbidity.

**Keywords:** Laparoscopy; hemodynamic instability; pheochromocytoma; adrenalectomy

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## Introduction

Pheochromocytomas are tumors arising from catecholamine producing chromaffin cells in the adrenal medulla (1). They almost always produce, store, metabolize and secrete catecholamines. Currently the only way to cure pheochromocytoma is its surgical removal. Roux and Mayo were the first to remove pheochromocytoma in 1926 and 1927, respectively (2). Unfortunately, due to the lack of understanding of pathophysiology of catecholamine secreting tumors and no antihypertensive medication adrenalectomy for pheochromocytoma was associated with extremely high mortality exceeding 50% (2). Only in 1956 priestly used alpha-blockers perioperatively which resulted in dramatic reduction in postoperative mortality (3). In 1996 Gagner *et al.* published a series of laparoscopic cases showing that minimally invasive access is safe and feasible (4). Over the last two decades adrenal gland surgery has transformed, so that laparoscopic access has become the gold standard

in the surgical treatment of adrenal tumors, including pheochromocytomas (5,6). The advances in operative technique and perioperative management have lowered mortality rates to 0–3% with complications occurring in 5% to 22% of patients (4,7–9). Although these numbers are now relatively low, perioperative hemodynamic instability still remains the biggest surgical and anesthetic challenge which apart from intraoperative bleeding is responsible for serious adverse events. The aim of this review was to discuss pre-, intra- and postoperative factors that may impact on hemodynamic condition of a patient.

## Preoperative management

Currently the gold standard in the assessment of adrenals before surgery includes imaging studies (computed tomography, magnetic resonance, <sup>131</sup>I-MIBG scintigraphy) (10,11). Additionally, hormonal activity of each tumor has to be evaluated. In case of pheochromocytoma urine

or plasma catecholamines and metanephrines levels are routinely used. Vanillylmandelic acid, although very specific for pheochromocytoma (95%) is characterized by rather low sensitivity (65%) (12). Both the size of the tumor and degree of catecholamines production correlates strongly with intraoperative hypertension (13). It is generally accepted that every patient with suspected pheochromocytoma requires appropriate preoperative optimization with antihypertensive drugs and blood volume expansion fluids. These precautions should be taken in every patient irrespective of clinical symptoms because undiagnosed pheochromocytoma or inadequately prepared patient may develop hypertensive crisis. In this situation mortality is close to 80% (14). In 1982 Roizen published a paper describing so-called Roizen criteria for adequate preoperative patient optimization with antihypertensive drugs (15). They include:

- (I) No in-hospital blood pressure >160/90 mmHg for 24 h prior to surgery;
- (II) No orthostatic hypotension with blood pressure <80/45 mmHg;
- (III) No ST or T wave changes for 1-week prior to surgery;
- (IV) No more than five premature ventricular contractions per minute.

The most commonly used drug for patients' preparation is phenoxybenzamine (irreversible, noncompetitive, alpha-blocker) (16,17). The initial therapy is introduced 10–14 days prior to surgery. The initial dose of phenoxybenzamine is 10 mg twice a day and is gradually increased until the clinical symptoms are controlled or side effects appear (usually the total daily dose is 1 mg/kg/d). Phenoxybenzamine can be administered intravenously or orally and the dose is increased every 48 hours (16,18). There are alternative  $\alpha$ -adrenoreceptor blockers such as: prazosin, terazosin and doxazosin. Although according to some studies they can be as effective as phenoxybenzamine, other studies did not support these conclusions (13,17). Moreover, in patients with coexisting tachyarrhythmia beta-blockers may be necessary. Currently, cardioselective beta1-blockers are preferred (metoprolol, atenolol) (18). In summary, appropriate preoperative alpha or/and beta-blockade allows significant reduction in cardiovascular morbidity and mortality as demonstrated by Goldstein *et al.* from 69% to 3% (19).

Although less effective, calcium channel blockers (amlodipine, nifedipine, nifedipine) are sometimes used as an alternative to alpha-blockers (16,18). However,

they are mostly combined with the latter in patients with uncontrolled hypertension despite alpha-blockade or as an alternative in patients with severe side-effects (18). In some hospitals they are also used as primary preoperative agent in normotensive patients with pheochromocytoma (7). Moreover, in some institutions catecholamine synthesis blockers are sometimes introduced (alpha-Methyl-L-tyrosine or metyrosine) (20–22). It significantly lowers the level of serum catecholamines (23). Although it has been shown to provide satisfactory results in blood pressure control preoperatively as well as intraoperatively (especially during induction of anesthesia or manipulation of the tumor when the most prominent catecholamines secretion occurs), its use is rather uncommon and reserved for patients with metastatic disease or as a combination with other alpha-blockers (21,22,24). According to previously published studies such combination allows better blood pressure stabilization, reduced intraoperative blood loss and volume replacement during surgery compared to alpha-blockers alone (21,22).

Interestingly, there are studies showing that preoperative medication seems unnecessary in case of pheochromocytoma. For instance, Boutros *et al.* basing on 63 cases suggested that pheochromocytoma patients can undergo successful surgery without preoperative alpha adrenergic blockade (25). Similar conclusions were drawn by Desmonts *et al.* (26). However, these results must be interpreted with caution. They comprise relatively small groups of patients with not entirely clear pre- and intraoperative anesthetic protocol, which does not allow drawing unequivocal conclusions.

Preoperative intravenous fluid administration before adrenalectomy for pheochromocytoma still remains the major dogma. In 1954 Thompson reported improved outcomes after whole blood transfusions at the level greater than estimated intraoperative blood loss (27). However, the surgery for pheochromocytoma at that time was associated with massive blood loss due to inadequate alpha-blockade and open approach. Later, Ulchaker reported zero mortality after 127 consecutive adrenalectomies in patients receiving intraoperatively large volumes of crystalloids and colloids (7). On the contrary, Gosse limited the amount of preoperatively administered fluids to 2,000 mL with satisfactory results (28). Moreover, Lebuffe *et al.* and Lentschener *et al.* transfused fluids intraoperatively only when blood pressure dropped during surgery (29,30). They did not report deaths related to hemodynamic instability. According to the most recent observations preoperative

intravenous fluid administration is not supported by any evidence-based study and does not improve outcomes in adrenalectomy for pheochromocytoma (17).

### Intraoperative considerations

As already mentioned surgery remains the only possible way to cure pheochromocytoma. The anesthetic protocol in this type of tumor has been previously extensively studied and it can be found elsewhere (16,31). There are several steps during surgery that are directly associated with sudden increase in blood pressure. They comprise changing the patient's position on the operating table; induction of general anesthesia and intubation; intraabdominal pressure changes (associated with cough, light sedation, and insufficient relaxation or initiation of mechanical ventilation); creation of pneumoperitoneum or when the tumor is directly manipulated (32-35). According to current recommendations laparoscopic or retroperitoneoscopic approach should be preferred since it has been shown to be safe also in cases of pheochromocytoma (6). Like in other surgical disciplines minimally invasive adrenalectomy is associated with reduced pain, decreased blood loss, faster recovery and shortened length of stay (36-39). Although it is generally accepted that tumors smaller than 6 cm are most suitable for laparoscopic removal, it has been shown feasible also in cases of bigger lesions (40). There are several studies documenting the use of robotic surgery in adrenal glands pathology. Although it is associated with additional costs the intraoperative blood loss and length of stay may be reduced comparing classical laparoscopy (41-44). Importantly, pheochromocytomas may also carry a malignant potential. We have demonstrated that laparoscopic access can be used also in cases of potentially malignant pheochromocytomas (PASS scale >6) and is not associated with inferior long-term outcomes (45). However, our observations suggest that surgery for pheochromocytoma is more difficult than for other adrenal tumors (46). Although the operative time was longer and blood loss was higher, complication rates remained unchanged. A study by Parnaby *et al.* showed that laparoscopic adrenalectomy for pheochromocytoma was indeed associated with increased episodes of severe intraoperative hypertension (SBP >200–220 mmHg) when compared to the laparoscopic resection of other adrenal tumors (47). Interestingly, a creation of peritoneum has been shown to increase catecholamines release which may result in hemodynamic instability (35,48,49). Moreover, case control studies confirmed that in terms of

hemodynamic instability laparoscopic approach is equal to open procedure (50,51). Moreover, a study by Kiernan *et al.* demonstrated that after open surgery the risk of increased number of episodes of systolic blood pressure >200 mmHg was 27 times higher comparing to laparoscopy (52). Minimally invasive surgery requires gentle, meticulous dissection. Otherwise uncontrolled bleeding precludes good visualization of proper surgical planes. This fits in perfectly with the principles of pheochromocytoma surgery that require minimal tumor manipulation to avoid excessive catecholamines release. On one hand increased levels of catecholamines result in the increase of blood pressure, on the other early adrenal vein ligation decreases their releasing into systemic circulation leading to sudden hypotension. Therefore, the anesthetist must be alerted and fully cooperate with the surgeon.

### Postoperative management

A large number of patients require vasopressor agents in the early period after tumor removal. The explanation of this phenomenon is on one hand high concentration of antihypertensive drugs, relatively low volume of circulating blood due to chronic vasospasm caused by catecholamines and their sudden decrease after surgery (13,48,52,53). Moreover, an association between down-regulation of alpha- and beta-adrenergic receptors caused by catecholamines and postoperative hypotension was observed (54,55). The rate of persistent postoperative hypotension varies between 30% and 60% and so far few studies focused on its risk factors (53,56-59). It has been shown that tumor size and preoperative levels of catecholamines (which correlate with tumor size) were associated with postoperative hemodynamic instability (53). According to Kiernan *et al.* the need for vasopressors was significantly higher after open procedures in univariate analysis (52). It was not confirmed in a multivariate model when the size of the tumor was additionally taken into consideration. Obviously open procedure is more often used in larger tumors, which are more hormonally active. Therefore, it is difficult to clearly answer the question whether it is really the type of surgery or the size of the tumor which in fact results in increased risk of hypotension after open procedure. On the contrary the study of Parnaby *et al.* comparing postoperative outcomes after laparoscopic adrenalectomy for pheochromocytoma *vs.* other tumors did not show any differences between groups (47). Although it may suggest that prolonged hypotension may occur irrespective of

hormonal status of the tumor, the study groups were small which does not allow explicit conclusions. In summary, the postoperative hypotension occurs relatively often after pheochromocytoma removal and may require postoperative use of vasopressors. It is strongly associated with tumor size and overproduction of catecholamines.

## Conclusions

In conclusion, hemodynamic instability is one of the most commonly diagnosed adverse events in patients undergoing laparoscopic adrenalectomy for pheochromocytoma. Although it occurs mostly during surgery, a significant proportion of patients require vasopressor agents also in the postoperative period. There are several risk factors associated with increased incidence of hemodynamic instability. They are directly related to the tumor size and its hormonal activity. Appropriate preoperative assessment and treatment with antihypertensive drugs significantly reduces the incidence of hemodynamic changes during and after surgery, thus minimizing serious complications and mortality. Moreover, operative factors seem to play crucial role. Meticulous dissection and gentle and minimal tumor manipulation and early adrenal vein ligation lower their incidence. Laparoscopy in the case of pheochromocytoma is safe and feasible. It is not associated with higher risk of hemodynamic instability. Such approach does not carry additional risk also in larger tumors. To minimize morbidity and mortality a close cooperation between the surgeon and anesthetist is mandatory in every patient with suspected or confirmed pheochromocytoma.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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